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INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT Article 36 and Rule 70)

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Applicant's or agent's file reference M/45063-PCT	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/IB 03/04502	International filing date (day/month/year) 15.08.2003	Priority date (day/month/year) 16.08.2002
International Patent Classification (IPC) or both national classification and IPC A61K39/395		
Applicant ABBOTT LABORATORIES (BERMUDA) LTD. et al.		

- This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
- This REPORT consists of a total of 7 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

 These annexes consist of a total of 4 sheets.

- This report contains indications relating to the following items:
 - I ☒ Basis of the opinion
 - II ☐ Priority
 - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
 - IV ☐ Lack of unity of invention
 - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
 - VI ☐ Certain documents cited
 - VII ☐ Certain defects in the international application
 - VIII ☐ Certain observations on the international application

Date of submission of the demand 15.03.2004	Date of completion of this report 14.02.2005
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EXAMINATION REPORT**

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I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-31 as originally filed

Claims, Numbers

1-23 received on 02.11.2004 with letter of 02.11.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

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III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 2-12, 23 (in part)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 2-12, 23 (in part) are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	6-12, 16, 20-23
	No: Claims	1-5, 13-15, 17-19
Inventive step (IS)	Yes: Claims	
	No: Claims	1-23
Industrial applicability (IA)	Yes: Claims	1-23
	No: Claims	

2. Citations and explanations

see separate sheet

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Item I

It would appear that amended **claims 1-23** filed with the letter dated 02.11.2004 do not introduce subject-matter which extends beyond the content of the application as filed and, thus, are considered to fulfil the requirements of **Article 34(2)(b) PCT**.

item III

1 Major Clarity problems (Article 6, PCT)

1.1 The Applicant argues that the features: aqueous pharmaceutical formulation having a shelf life of at least 18 months/ (part (a) and (b) of **claim 1**); aqueous pharmaceutical formulation which maintains stability following at least 3 freeze/thaw cycles of the formulation (part c. of **claim 1**); having enhanced stability of at least 12 months at a temperature of 2-8°C (part (d) of **claim 1**) combined with the characteristics of having a pH between 4-8 and that formulation comprises an Ab would recite the essential features of the invention.

However the International Preliminary Examination Authority is still of the opinion that what the applicant is trying to claim is a desired result, rather than the manner of achieving the result, which is what the invention should normally correspond to.

Claim 1 and dependent **claims 2-12** refer to a pharmaceutical formulation characterized merely by statements of the problem(s) to be solved, i.e. having a shelf life of at least 18 month (in the liquid state), maintains stability following at least 3 freeze/thaw cycles of the formulation and having enhanced stability of at least 12 months at a temperature of 2-8°C.

It is clear from the description that the specific formulation(s) disclosed in the examples is(are) essential to obtain the desired result(s) (c.f. example 1). Since neither independent **claim 1** nor one of its dependent **claims 2-12** contain these essential technical features they do not meet the requirement following from **Article 6, PCT** taken in combination with **Rule 6.3(b), PCT** that any independent claim must contain all the technical features essential to the definition of the invention.

1.2 Some of the features in compound **claim 23** relate to a method of using the claimed compound(s) rather than clearly defining the compound(s) in terms of its technical features. The intended limitations are therefore not clear from this claim, contrary to the requirements of **Article 6 PCT**.

item V

2 Reference is made to the following documents:

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- D1** US-A-6 024 938 (BORNSTEIN MICHAEL ET AL) 15 February 2000 (2000-02-15)
D2 EP-A-1 174 148 (YAMANOUCHI PHARMA CO LTD) 23 January 2002 (2002-01-23)
D3 US-A-6 090 382 (HOOGENBOOM HENDRICUS R M ET AL) 18 July 2000 (2000-07-18)
cited in the application
D4 Holt-LJ et al., Domain antibodies: proteins for therapy. Trends in Biotechnology, 21(11):
484-490 (November 2003)

3 Novelty (Article 33(2), PCT)

The Applicant was not able to overcome the novelty objections concerning **D1**.

Concerning **D2** the International Preliminary Examining Authority agrees with the arguments of the applicant, i.e. that **D2** discloses "only" an Ab-fragment, i.e. Fab, and thus can not destroy the novelty of a formulation comprising an Ab.

- 3.1 D1** discloses a pharmaceutical formulation comprising 1 mg/ml SHNH-IgG, 0,9% saline, 1,25% maltose (can be replaced by mannitol; both are drying protectants), polysorbate 80 (0,01%, Tween), citrate buffer (20 nM) with pH 5.2. Accordingly, the formulation is lyophilized and may be stored stably for extended periods of time. The reagents may be provided in the form of kits having the advantage of providing a stable formulation with a long shelf life (c.f. abstract; column 9, l 4-29; c 11, last §).

remark 1: before lyophilization, the formulation is in a liquid, aqueous state.

ie. **D1** discloses an aqueous pharmaceutical composition comprising a polyol (12.5 mg/ml maltose or mannitol), a surfactant (0.01 % = 0.1 mg/ml polysorbate 80), and a buffer system comprising citrate with pH 4-8 and 1 mg/ml of an Ab ("comprising an Ab" is considered to include also linked-Ab).

The functional features concerning the stability of the solution are not mentioned in **D1**, however, it is assumed, that the pharmaceutical formulation of **D1** has the same properties.

Therefore, the teachings of **D1** would appear to anticipate the subject matter of **claims 1, 3-5, 14-15, 17-19** in the sense of **Article 33(2), PCT**.

- 3.2** It would appear that no documents are comprised in the known prior art, specifically disclosing an aqueous pharmaceutical composition comprising a polyol, a surfactant, and a buffer system comprising citrate and/or phosphate with a pH of 4-8, in amounts to formulate an Ab which binds human TNF-alpha for therapeutic use at a concentration of >45 mg/ml.

Thus, the subject matter of **claims 2, 6-13, 16, 20-23**, as far as being clear (c.f. item III above) would appear to be novel in the sense of **Article 33(2), PCT**.

4 Inventive step (Article 33(3), PCT)

Due to the lack of essential technical features (c.f. item III, above) and/or novelty, it is not possible to acknowledge an inventive step for the subject matter of **claims 1-12**.

The subject matter of **claims 13, 16, 20-23** would not appear to involve an inventive step in the sense of **Article 33(3), PCT** for the following reasons:

D3 is considered to be the closest prior art and discloses rec. human anti-TNF-alpha Ab with high affinity for hTNF alpha (e.g., $K_d=10^{-8}$ M or less), a slow off rate for hTNF alpha dissociation (e.g., $K_{off}=10^{-3}$ sec⁻¹ or less), neutralizing hTNF alpha activity in vitro and in vivo. One specific Ab disclosed is D2E7, moreover all specific anti-TNF-alpha molecules of **claims 6-12** of the application are disclosed. The use of PBS, isotonic agents (e.g. mannitol), emulsifying agents etc. or surfactants is mentioned. **D3** mentions that many methods for the preparation of such formulations are patented or generally known to those skilled in the art and refers to e.g., Sustained and Controlled Release Drug Delivery Systems, J. R. Robinson, ed., Marcel Dekker, Inc., New York, 1978 (c.f. col 21, l 1-6, 23, 49; col 23, l 62-67; claims 1-10).

The difference between the subject matter of **claims 16** and **D3** is that the formulation of **claim 13** is used for an anti-TNF-alpha Ab.

The technical problem is to provide a pharmaceutical formulation for an anti-TNF-alpha Ab. The claimed solution is the specific formulation of **claim 13**.

Suitable Ab formulations are known in the art c.f. e.g. **D1** or **D2**:

D1 discloses a pharmaceutical formulation comprising 1 mg/ml SHNH-IgG, 0,9% saline, 1,25% maltose (can be replaced by mannitol; both are drying protectants), polysorbate 80 (0,01%, Tween), citrate buffer (20 nM) with pH 5.2. Accordingly, the formulation is lyophilized and may be stored stably for extended periods of time. The reagents may be provided in the form of kits having the advantage of providing a stable formulation with a long shelf life (c.f. abstract; column 9, l 4-29; c 11, last §).

D2 discloses a Fab fragment preparation comprising 1) 0.01 - 10 mg/ml Fab fragment, 2) 0.01-50% sucrose and/or mannitol, 3) 0.0001-0.1% of anionic surface active agent (polysorbate 80; reported to reduce aggregate formation induced by physical stress), 4) 1-500 mM of a buffer (phosphate or citrate buffer), 4) having pH 4-6. Accordingly, the stable parenteral composition has no using limitations such as cold place preservation avoiding freezing, transfer and handling avoiding shaking (c.f. abstract; § 28; § 31; claims 1, 5, 6, 8-

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10).

It is obvious that different Ab or Ab-fragments can be formulated in such a composition. Combining the teachings of **D1** and/or **D2** with the closest prior art, the skilled person has clear indications for substances to be used in formulations suitable for anti-TNF alpha Ab, i.e. a polyol a surfactant and a buffer system comprising citrate and/or phosphate with a pH 4-6. Applying trivial routine testing it would be easy for a skilled person to determine the optimal formulation for a given Ab in desired amounts.

As the compositions disclosed in **D1** or **D2** comprise all specific ingredients in concentrations claimed in the present application to be necessary for obtaining the desired TNF-alpha Ab formulation it is assumed that those formulation (**D1** and **D2**) also have the claimed functional features.

Although **D1** or **D2** do not specify the specific composition of their citrate buffers, suitable compositions for the formulation of Ab in a solution with a given pH are well known in the art.

Thus, the subject matter of **claims 13, 16, 20-23** would not appear to involve an inventive step in the sense of **Article 33(3), PCT**.

5 further remarks:

5.1 The vague statements in the description on page 28, line 1-2 and page 31, line 25-28 imply that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (**Article 6, PCT**) when used to interpret them (see also the **PCT Guidelines, III-4.3a**).

5.2 The repeated use of the non restrictive term/phrase "about", "...about...to about..." or similar terms introduces ambiguity into **claims 1, 3, 4, 13, 18, 19, 20** their dependent claims and the description (e.g. page 22, line 5-11 etc.) (c.f. **PCT Guidelines, Section IV, III-4.5a**). Defining the term "amount" as "reasonably close to" underlines the vague subjective nature of the term.

5.3 In a later European regional phase objections might be raised against any expression within the description such as "...incorporated by reference..." (e.g. on page 15, line 22; p 16, l 28; p 20, l 9, 17; p 23, 15, 19; p 28, l 2-5; p 31, l 19, 20) as the regional patent law requires that the application is self-contained.

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What is claimed is:

1. A pharmaceutical formulation selected from the group consisting of:
 - 5 (a) a liquid aqueous pharmaceutical formulation comprising a therapeutically effective amount of an antibody in a buffered solution, said formulation having a pH between about 4 and 8 and having a shelf life of at least 18 months;
 - 10 (b) an aqueous pharmaceutical formulation comprising a therapeutically effective amount of an antibody in a buffered solution, said formulation having a pH between about 4 and 8 and having a shelf life of at least 18 months in the liquid state;
 - 15 (c) a liquid aqueous pharmaceutical formulation comprising a therapeutically effective amount of an antibody in a buffered solution, said formulation having a pH between about 4 and 8 which maintains stability following at least 3 freeze/thaw cycles of the formulation; and
 - 20 (d) a liquid aqueous pharmaceutical formulation comprising a therapeutically effective amount of an antibody in a buffered solution, said formulation having a pH between 4 and 8 and having enhanced stability of at least 12 months at a temperature of 2 - 8°C.
- 25 2. The formulation of claim 1, wherein the antibody is directed to TNF α .
3. The formulation of claim 1, wherein the concentration of the antibody is between about 1-150 mg/ml.
- 30 4. The formulation of claim 1, wherein the concentration of the antibody is about 50 mg/ml.
5. The formulation of claim 1, which further is suitable for single use subcutaneous injection.
- 35 6. The formulation of claim 1, wherein the antibody is an antibody, or an antigen-binding portion thereof, that dissociates from human TNF α with a K_d of $1 \times 10^{-}$

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⁸ M or less and a K_{off} rate constant of $1 \times 10^{-3} \text{ s}^{-1}$ or less, both determined by surface plasmon resonance, and neutralizes human TNF α cytotoxicity in a standard *in vitro* L929 assay with an IC_{50} of $1 \times 10^{-7} \text{ M}$ or less.

5 7. The formulation of claim 6, wherein the antibody, or antigen-binding portion thereof, is a recombinant antibody, or antigen-binding portion thereof.

10 8. The formulation of claim 1, wherein the antibody is an the antibody, or antigen-binding portion, thereof which:

a) dissociates from human TNF α with a K_{off} rate constant of $1 \times 10^{-3} \text{ s}^{-1}$ or less, as determined by surface plasmon resonance;

15 b) has a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, or modified from SEQ ID NO: 3 by a single alanine substitution at position 1, 4, 5, 7 or 8 or by one to five conservative amino acid substitutions at positions 1, 3, 4, 6, 7, 8 and/or 9;

20 c) has a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12.

25 9. The formulation of claim 1, wherein the antibody, or antigen-binding portion thereof, has a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 2.

30 10. The formulation of claim 1, wherein the antibody, or antigen-binding portion thereof, neutralizes the activity of human TNF α , chimpanzee TNF α and at least one additional primate TNF α selected from the group consisting of baboon TNF α , marmoset TNF α , cynomolgus TNF α and rhesus TNF α .

11. The formulation of claim 1, wherein the antibody, or an antigen-binding portion thereof, also neutralizes the activity of mouse TNF α and/or pig TNF α .

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12. The formulation of claim 1, wherein the antibody, or antigen-binding portion thereof, binds human TNF α and is the antibody D2E7 or an antigen binding portion thereof.
- 5 13. An aqueous pharmaceutical composition comprising a polyol, a surfactant, and a buffer system comprising citrate and/or phosphate with a pH of about 4 to 8, in amounts sufficient to formulate an antibody for therapeutic use at a concentration of greater than about 45 mg/ml.
- 10 14. The composition of claim 13, wherein the polyol is mannitol and the surfactant is polysorbate 80.
- 15 15. The composition of claim 14, which contains 5-20 mg/ml of mannitol and 0.1-10 mg/ml of polysorbate 80.
- 20 16. The formulation of claim 13, which contains an antibody, or antigen-binding portion thereof, which binds human TNF α and is the antibody D2E7 or an antigen binding portion thereof.
- 25 17. A liquid aqueous pharmaceutical formulation comprising
(a) 1-150 mg/ml of antibody,
(b) 5-20 mg/ml of mannitol,
(c) 0.1-10 mg/ml of Tween-80, and
(d) a buffer system comprising citrate and/or phosphate, with a pH of 4 to 8.
- 30 18. The formulation of claim 17, wherein the pH is selected from the group consisting of between about 4.5 to about 6.0, between about 4.8 to about 5.5, and between about 5.0 to about 5.2.
- 35 19. The liquid aqueous pharmaceutical formulation of claim 17, which contains
(a) about 50 mg/ml of antibody,
(b) about 12 mg/ml of mannitol,
(c) about 1 mg/ml of Tween-80, and

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(d) a buffer system comprising citrate and/or phosphate with a pH of about 4 to about 8.

- 5 20. The formulation of claim 17, wherein the buffer system comprises
- (a) about 1.3 mg/ml of citric acid,
- (b) about 0.3 mg/ml of sodium citrate,
- (c) about 1.5 mg/ml of disodium phosphate dihydrate,
- 10 (d) about 0.9 mg/ml of sodium dihydrogen phosphate dihydrate, and
- (e) about 6.2 mg/ml of sodium chloride.
21. The formulation of claim 19, wherein the antibody is directed to TNF α .
- 15 22. The formulation of claim 19, wherein the antibody, or antigen-binding
- portion thereof, binds human TNF α and is the antibody D2E7 or an antigen binding
- portion thereof.
- 20 23. The formulation of claim 22, which is administered to a subject suffering
- from a disorder in which TNF α activity is detrimental such that TNF α activity in the
- subject is inhibited.
- 25